Remarks

Claims 127-132 are pending in this application. Claim 127 is amended in this paper to recite, in part, that the second compound is used for the treatment or prevention of an affective disorder. Support for this amendment can be found, for example, page 5, lines 12-20 of the specification. No new matter has been introduced.

A. The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn

On pages 3-4 of the Office Action and in the Advisory Action, claims 127-130 are rejected as allegedly anticipated by U.S. Patent No. 6,274,579 ("the '579 patent") or 6,391,875("the '875 patent"), and/or U.S. Publication No. 2003/0064988 ("the '988 publication"), all to Morgan *et al.*[1] Applicants respectfully traverse this rejection.

In response to Applicants' submission that the claims are not anticipated because the '579 or '875 patent does not disclose the administration of a bupropion metabolite adjunctively with a pharmacologically active second agent, as recited by claim 127, the Examiner points to two portions in the cited references in support of the proposition that the use of second agent has been disclosed: 1) col. 7, line 38 - col. 8, line 20 of the '579 patent; and 2) paragraph 20 of the '988 publication. (Advisory Action, page 2).

The first portion referred to by the Examiner, *i.e.*, col. 7, line 38 - col. 8, line 20 of the '579 patent, discloses what is termed as "tetrabenazine-induced behavioural depression experiment," wherein tetrabenazine is administered to animals to induce depression solely to create a model system for depression. (*See* the '579 patent, col. 7, lines 38-60). The Examiner, based on this disclosure, alleges that the use of second active agent has been disclosed in the '579 patent because "the claims are only requiring a therapeutically effective amount of second active agent but fail to limit the specific therapeutic utility" of the second active agent. (Advisory Action, page 2).

Applicants respectfully disagree with the Examiner's allegation. In particular, because claim 127 specifically recites the treatment or prevention of an

[1] The '579 and '875 patents are equivalents. The '988 publication is a continuation-in-part of the '875 patent, which contains matters not disclosed in the '579 and '875 patents, as discussed below.

affective disorder, therefore, the recitation of "therapeutically or prophylactically effective amount" of the second agent clearly means that the second agent is used for the treatment or prevention of the affective disorder. However, solely to expedite the prosecution of this application, Applicants amended claim 127 to recite, in part, the use of a second pharmacologically active compound is "for the treatment or prevention of said affective disorder." In view of this amendment, Applicants respectfully request that the rejection be withdrawn.

With regard to the second portion referred to by the Examiner, *i.e.*, paragraph 20 of the '988 publication, Applicants respectfully point out that the subject matter disclosed in that portion is added in the '988 publication for the first time, *i.e.*, the parents (the '579 and '875 patents) do not contain that specific subject matter. Therefore, the priority date of the particular subject matter referred to by the Examiner is May 17, 2002 (the filing date of the '988 publication), and thus, that particular subject matter is not prior art to the present application. Therefore, Applicants respectfully point out that the rejection under 35 U.S.C. § 102, based on the paragraph 20 of the '988 publication, cannot be sustained.

Consequently, Applicants respectfully submit that the pending claims are not anticipated, and thus, respectfully request that the rejection of the claims be withdrawn.

B. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

On pages 4-5 of the Office Action and in the Advisory Action, claims 131-132 are rejected as allegedly obvious over the '875 patent in view of U.S. Patent No. 6,677,378 to Howard *et al.* ("the '378 patent") or WO 99/17803 by Cary ("the '803 publication"), which supposedly show "the conventional knowledge available in the field at the time of the invention." (*See* Advisory Action, page 2). Applicants respectfully traverse this rejection. Specifically, Applicants respectfully submit that no *prima facie* case of obviousness is established by the references cited by the Examiner.

In particular, it is alleged that because the '875 patent discloses the use of (S,S)-hydroxybupropion for the treatment of certain affective disorders, "it would have been obvious ... to combine secondary active agent to improve the therapeutic efficacy because the combination drug therapy is known as standard drug regimen for

the treatment of psychotic conditions or other affective conditions." (Office Action, page 5). Applicants respectfully disagree.

Applicants point out that a motivation or suggestion to modify the disclosure of '875 patent did not exist prior to this invention. This is because, while disclosing certain uses of (S,S)-hydroxybupropion, the '875 patent is completely silent regarding combining it with any other active agent(s), much less SSRI, 5-HT_3 inhibitor or nicotine, as claims 131-132 recite. In addition, there is no disclosure whatsoever in the '875 patent regarding the desirability of combining (S,S)-hydroxybupropion with any second active agent. Despite this fact, the Examiner, relying on the '378 patent or the '803 publication, alleges that "the conventional knowledge available in the field at the time of the invention was filed ... renders the claimed subject matter obvious." (Advisory Action, page 2). Applicants respectfully disagree for at least the following reasons.

The '378 patent, by disclosing a genus of compounds completely different from the compounds recited by the pending claims, provides no specific suggestion or motivation to arrive at the claimed invention. The Examiner refers to the '378 patent to support the proposition that "combination drug therapy is routinely practiced in the treatment of affective disorders." (Office Action, page 5). However, Applicants respectfully point out that the fact that "combination drug therapy is routinely practiced," even if taken true, has nothing to do with the patentability of the pending claims. This is because such a general statement cannot provide any specific suggestion or motivation to those of ordinary skill in the art with regard to <u>any combination therapy</u>, much less the combination of the specific compound (a bupropion metabolite) with the specific second agent (an SSRI, a 5-HT_3 inhibitor, or nicotine), as recited by claim 131. At most, the '378 patent's disclosure is an invitation to experiment, which is a legally improper basis for rejection a claim under obviousness.[2] (*See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986)).

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[2] Applicants respectfully submit that the '378 patent's disclosure even falls short of an invitation to experiment because the statement made in the '378 patent is simply too general. Under the Examiner's logic, *i.e.*, the claims to the use of a specific combination is obvious over a disclosure that "combination therapy is routinely practiced," all claims to any combination therapy would be held *prima facie* obvious.

Likewise, the '803 publication does not provide any specific suggestion or motivation because there is no disclosure whatsoever in the '803 publication regarding a bupropion metabolite. Further, while the '803 publication discloses that various antidepressants can allegedly be combined with a nicotine receptor antagonist, there is no disclosure in the '803 publication that bupropion, much less a bupropion metabolite, is any more or less effective than other antidepressants.[3]

Finally, Applicants again respectfully invite the Examiner's attention to Post *et al.*, *Depression and Anxiety*, 5(4): 175-189 (1997) ("Post"), which was cited in the Office Action and was discussed in Applicants' previous response thereto. Applicants respectfully point out that Post provides a glimpse of what was known in the art at the time of this invention with regard to combination therapies, and attests to the fact that the claimed invention is not obvious.

Post discloses, referring to combination therapies for bipolar depression, that there are "a panoply of treatment options now exist," and states that these potential therapies' "relative efficacy in different illness subtypes and stages remains to be better delineated, as do their optimal sequencing and use in combination in individual patients." (Post, page 184, under "Summary and Conclusion") (emphasis added). In addition, Post states that when using combination therapies, "one has to be particularly careful about drug interactions and their potential for toxicity as well as therapeutic effects." (*Id.*). Post also teaches that "one should be aware of potential pharmacokinetic interactions" when using a combination therapy. (*Id.*). As can be seen from these statements, Post clearly teaches that no generalization can be made regarding any specific combination therapies for affective disorders. Consequently, by disclosing that no generalization can be made, Post suggests the non-obviousness of specific combination therapies that may be used to treat affective disorders.

Along the same line, Post evidences the fact that there would have been no reasonable expectation of successfully making and using the claimed

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[3] Even assuming, arguendo, that the '803 publication somehow did suggest that bupropion is more effective than other antidepressants, such a disclosure does not specifically suggest the combination of a bupropion metabolite and a second active agent as recited by the pending claims because it was well-known at the time of this invention that the efficacy of any specific combination cannot be generalized, as discussed below.

combinations. As discussed above, Post teaches that various factors must be given careful considerations when combination therapies are attempted. Therefore, those of ordinary skill in the art would have had no expectation, much less a reasonable expectation, of successfully making and using any combination of agents, much less the combinations recited by the claims.

In sum, Applicants respectfully submit that no *prima facie* case of obviousness is established by the references cited by the Examiner[4] because: 1) no specific motivation or suggestion is provided in the cited references with regard to the claimed method using the specific combination; and 2) the fact that it was well-known in the art that no generalization can be made with regard to any specific combination of therapeutics would not have provided reasonable expectation of successfully making and using the claimed invention to those skilled in the art. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

C. The Double Patenting Rejection Should Be Withdrawn

On pages 5-6 of the Office Action, the claims are provisionally rejected under judicially created non-statutory double patenting as allegedly unpatentable over the claims in the co-pending Application No. 09/987,930 ("the '930 application"). Applicants respectfully pointed out in their previous response that the claims in these two cases are directed to different subject matter. (*See* Applicants' Response of January 18, 2006, page 8). As this submission is not disputed in the Office Action, Applicants respectfully request that this rejection be withdrawn.

[4] And thus, no need for the showing of "unexpected results," as required by the Examiner. (*See* Advisory Action, page 2).

Conclusion

Applicants respectfully submit that all of the pending claims are allowable, and request that rejections directed to the claims be withdrawn.

No fee is believed due for this submission. Should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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